Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Initially, applicant would like to note that the present amendment is being submitted in compliance with "Amendments In A Revised Format Now Permitted", 1267 OG 4 (February 25, 2003). Pursuant to this notice, the requirements of 37 C.F.R. § 1.121 have been waived.

The rejection of claims 1, 2, and 8-12 under 35 U.S.C. § 112 (second paragraph) is respectfully traversed in view of the above amendments.

The rejection of claim 1 under 35 U.S.C. § 102(b) as being anticipated by Magnussen et al., "Heme Oxygenase-1, Heme Oxygenase-2 and Biliverdin Reductase in Peripheral Ganglia from Rat, Expression and Plasticity," *Neuroscience* 95(3):821-829 (2000) ("Magnussen"), as evidenced by Agiro et al., "A Quantitative Study of Growth Con Filopodial Extension." *J. Neurosci. Res.* 13:149-162 (1985) ("Agiro"), is respectfully traversed.

Magnussen examines the expression of heme oxygenase-1 (HO-1), heme oxygenase-2 (HO-2), and biliverdin reductase (BVR) in ganglia excised from sacrificed rats, which ganglia were immersed in tissue culture for 0 to 48 hours before being fixed and immunostained using antibodies specific to HO-1, HO-2, and BVR.

The PTO merely cites to Agiro as evidence that superior ganglion cells undergo changes in structure in culture. However, Agiro utilized a medium containing 10% placental serum and nerve growth factor (page 152) and therefore one of ordinary skill in the art would have expected the cultured cells to undergo structural changes given the presence of the nerve growth factor. In contrast, Magnussen reports using serum free RPMI 1640 medium, which does not include nerve growth factor. Because Magnussen and Agiro did not culture the ganglia in the same culture medium, Agiro does not provide evidence the cultured cells of Magnussen would inherently have a modified cell structure.

Moreover, Magnussen does not teach or suggest "introducing into a mammalian cell either biliverdin reductase or a fragment or variant thereof, or a nucleic acid molecule encoding biliverdin reductase or a fragment or variant" as recited in claim 1, let alone the modifying of cell structure by causing "enhanced cell size, actin microspike formation, polar cell morphology, or a combination thereof" as recited in claim 1.

For these reasons, the rejection of claim 1 as anticipated by Magnussen is improper and should be withdrawn.

The rejection of claims 1 and 8-12 under 35 U.S.C. § 103(a) for obviousness over Lagarias et al., "Regulation of Photomorphogenesis by Expression of Mammalian Biliverdin Reductase in Transgenic Arabidopsis Plants," *Plant Cell* 9:675-688 (1997) ("Lagarias") in view of Ausubel et al., *Current Protocols in Molecular Biology* (online version), Unit 16.12 "Overview of Protein Expression in Mammalian Cells" (2002) ("Ausubel") and Panahian et al., "Enhanced Neuronal Expression of the Oxidoreductase – Biliverdin Reductase – After Permanent Focal Cerebral Ischemia," *Brain Res.* 850:1-13 (1999) ("Panahian"), is respectfully traversed.

Lagarias reports the construction of transgenic Arabidopsis that express a BVR variant (see page 676). Lagarias also describes the effects of the variant BVR expression, which changed the levels of linear tetrapyrrole intermediates committed to the synthesis of the phytochrome chromophore (pages 676). Phenotypes displayed by the transgenic plants included chlorotic, elongated stems and petioles, and early bolting, all of which are consistent with phytochrome-deficiency (page 677). Thus, phytochrome deficiencies were the direct cause of the altered phenotypes.

While Ausubel is not available as prior art (the PTO cited to the 2002 online version), applicant does not dispute that transfection of mammalian cells is known in the art.

Panahian reports on the time-dependent changes in the level of BVR following permanent middle cerebral artery occlusion in mice (abstract). Panahian indicates that an increase in BVR was detected in ischemic penumbra and that this may represent an important factor in protection against bilirubin neurotoxicity (abstract). The PTO specifically cites to Panahian for suggesting that "BVR expression is a possible new direction for protecting neurons against ischemic injury and oxidative stress" (abstract).

Applicant submits that one of ordinary skill in the art would not have combined the teachings of Lagarias and Panahian because the two references are not analogous art. In determining whether a reference constitutes "analogous art", the Federal Circuit has set forth a two-part test inquiring:

> (1) whether the art is from the same problem solving field of endeavor, and (2) if the reference is not within the field of the inventor's endeavor, whether the reference is still reasonably pertinent to the particular problem with which the inventor is involved.

See In re Clay, 966 F.2d 656, 658-659, 23 USPQ2d 1058, 1060-1061 (Fed. Cir. 1992).

The problem solving area of the present invention relates to modifying mammalian cell structure using BVR. Neither Lagarias nor Panahian relates to the problem solving field. While Panahian at least reports on research involving mammals, Lagarias clearly does not. As noted above, Lagarias involves the transformation of Arabidopsis plants with a variant BVR-encoding nucleic acid. Although plant tissues were modified in their structure and their properties, such modifications were consistent with phytochrome deficiency caused by BVR disruption of phytochrome production. Phytochromes are pigments that are present in most plants and mediate many light-dependent processes. Because mammalian cells and plant cells are distinctly different (i.e., plant cells normally contain phytochromes), one of ordinary skill in the art would not have considered the report of Lagarias pertinent to working with mammalian cells as with Panahian. Therefore, the teachings of Lagarias and Panahian are not properly combined.

Assuming *arguendo* that Lagarias and Panahian can be combined (which applicant does not admit), applicant submits that the combination of references fails to provide the requisite motivation to combine the teachings, fails to provide any expectation of success in modifying mammalian cell structure, and fails to teach or suggest each and every limitation of the presently claimed invention.

The PTO cites to Panahian as motivation to try moderating BVR expression levels in mammalian cells, but Panahian merely indicates that modulating BVR expression is "a *possible* new direction" (emphasis added). Thus, Panahian is tantamount to an invitation to experiment and as such fails to provide the requisite motivation.

Because Panahian is silent with regard to the effect of BVR (or fragment or variant) levels on cell structure and Lagarias only discloses the effects of heterologous variant BVR on plant cells (affording phenotypes consistent with phytochrome deficiencies), one of ordinary skill in the art is left to speculate whether introducing BVR (or a fragment or variant thereof) into mammalian cells or transforming mammalian cells with a nucleic acid encoding BVR (or a fragment or variant thereof) can indeed modify the cellular structure of treated mammalian cells. The PTO has failed to identify how the combination of references would lead one of ordinary skill in the art to expect to be successful in modifying mammalian cell structure when carrying out the presently claimed invention, given that heterologous BVR in plant cells disrupted a distinct plant cell biochemical pathway.

Finally, the combination of references fails to teach or suggest the presently claimed method of modifying the cellular structure of mammalian cells by introducing BVR (or a fragment or variant thereof) into mammalian cells or transforming mammalian cells with a nucleic acid encoding BVR (or a fragment or variant thereof). As noted above,

Panahian provides nothing more than a general incentive to explore moderating BVR levels in mammalian cells. But it is well established that the existence of a general incentive to investigate does not make the result of such investigation obvious. See In re Deuel, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995) ("'[o]bvious to try' has long been held not to constitute obviousness"). Moreover, the combination of references does not teach or suggest causing "enhanced cell size, actin microspike formation, polar cell morphology, or a combination thereof" as recited in claim 1. Thus, it would not have been obvious to modify mammalian cell structure in accordance with the presently claimed invention.

For all these reasons, the rejection of claims 1 and 8-12 for obviousness over Lagarias in view of Ausubel and Panahian is improper and should be withdrawn.

The rejection of claims 1, 2, and 8-12 under 35 U.S.C. § 112 (first paragraph) for lack of enablement is respectfully traversed in view of the above amendments and the following remarks.

Applicant appreciates the acknowledgement at page 5 of the outstanding office action that the present invention enables modifying cell structure with expression of exogenous BVR in HeLa cells to afford enhanced cell size, actin microspike formation, or polar cell morphology. Based on the above amendments, therefore, the only issues remaining concern (1) the use of fragments or variants of BVR; and (2) modifying cell structure in cells other than HeLa cells.

Applicant notes that the present application does indeed identify two human BVR variants (SEQ ID NO: 1 and SEQ ID NO: 3) and the encoding nucleic acid molecule for the first variant. Given the similarity between the two proteins and the provision of the nucleic acid molecule of SEQ ID NO: 2, one of ordinary skill in the art could prepare desired point mutations in SEQ ID NO: 2 to arrive at a nucleic acid encoding the protein of SEQ ID NO: 3. In addition, the present application identifies a rat BVR of SEQ ID NO: 4 (encoded by nucleic acid of SEQ ID NO: 5). In addition, the specification recites that other mammalian BVR nucleic acids (and their encoded proteins) can be identified following the performance of nucleic acid hybridization between the nucleic acid of SEQ ID No: 2 or SEQ ID NO: 5 and, e.g., genomic DNA from another mammal (see paragraph bridging pages 9-10).

At page 9, first paragraph, the specification identifies the structural features of BVR and at page 10, lines 15-27, the specification indicates that fragments can be prepared using known technique to obtain a fragment of BVR that preferably contains one or more of the previously identified functional domains (and possesses one or more of the activities of

full length BVR). Thus, the present application does in fact define the fragments of BVR. In addition, the present application refers to (and incorporates in its entirety) co-pending U.S. Patent Application Serial No. 09/606,129 to Maines, filed June 28, 2000, as identifying a number of BVR variants. As described therein, specific variants of SEQ ID NO: 1 include one or more of (i) $Gly^{17} \rightarrow$ Ala within the nucleotide binding domain, (ii) $Ser^{44} \rightarrow$ Ala within one of the kinase motifs, (iii) $Ser^{149} \rightarrow$ Ala within the kinase motif of the leucine zipper, (iv) $Cys^{74} \rightarrow$ Ala within a substrate binding domain, (v) $Lys^{92}His^{93} \rightarrow$ Ala-Ala within the oxidoreductase motif, (vi) $G^{222}LKRNR^{227} \rightarrow$ VIGSTG within the nuclear localization signal, and (vii) $Cys^{281} \rightarrow$ Ala within the zinc finger domain, and (viii) $Lys^{296} \rightarrow$ Ala at the C terminus within a substrate binding domain (i.e., protein kinase inhibitory domain).

In vitro and *in vivo* methods for introduction of BVR (or fragments or variants thereof) as well as nucleic acid molecules encoding the same into mammalian cells is described at pages 13-17 and in Example 1. In addition, the present application specifies at page 20 that mammalian cells whose structure can be modified include stem cells (both omnipotent and pluripotent stem cells), neuronal or glial cells, vascular smooth muscle cells, skeletal muscle cells, epithelial cells, and nucleated blood cells (e.g., macrophages and other blood cells). Example 1 specifically describes structural modification of an epithelial (HeLa) cell by transformation of the cell with a nucleic acid encoding BVR and identifies two putative pathways that can stimulate the changes observed in the treated epithelial (HeLa) cells. These specific pathways involve Cdc42 kinase, which is known to stimulate spike formation, and D type cyclins, e.g., cyclin D_2, which is known to deregulate cell size and cause cell mass increase.

Given the description of the materials and techniques for practicing the present invention and applicant's success in practicing the invention with epithelial (HeLa) cells, as well as the identification of two putative pathways that regulate the specific modified cell structures as described by applicant, applicant submits that one of ordinary skill in the art is fully able to perform to presently claimed invention in any mammalian cell using BVR as well as fragments or variants thereof.

For the foregoing reasons, applicant respectfully submits that the rejection of claims 1, 2, and 8-12 for lack of enablement of enablement is improper and should be withdrawn.

The rejection of claim 1, 2, and 8-12 under 35 U.S.C. § 112 (first paragraph) for lack of written descriptive support is respectfully traversed in view of the above amendments and the following remarks.

As noted above, the specification identifies a number of BVR variants and describes BVR fragments, as well as evidences successful modification of cell structures (including enhanced cell size, actin microspike formation, and polar cell morphology) in epithelial (HeLa) cells.

The written description requirement for a claimed genus can be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics. See 66 Fed. Reg. 1099, 1106 (January 5, 2001). What constitutes a "representative number of species" will vary from case to case, dependent upon whether the applicant was in possession of the necessary common attributes or features of member of the genus. In this case, the single representative species relates to exogenous expression of a transgene encoding BVR in an epithelial (HeLa) cells, which displayed enhanced cell size, actin microspike formation, and polar cell morphology (see Example 1). Given applicant's reduction to practice and the presence of written descriptive support in the application for variants and fragments of BVR that can be utilized, other cell types whose structure can be modified (with regard to enhanced cell size, actin microspike formation, or polar cell morphology), and several putative biochemical pathways that can stimulate the changes observed in the epithelial (HeLa) cells, one of ordinary skill in the art would fully appreciate that applicant was in possession of the presently claimed genus as defined by claims 1 and 8-12 as amended.

In addition to the foregoing, applicant would like to bring to the attention of the PTO co-pending U.S. Patent Application Serial No. 09/606,129 to Maines, filed June 28, 2000 (noted above as being cited and incorporated by reference into the specification of the present application).

In view of all of the foregoing, applicant earnestly submits that this case is in condition for allowance.

Respectfully submitted,

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